Doctors notes, extra notes for explanation

Disease of adrenal gland

1. HYPERCORTISOLISM (CUSHING SYNDROME):
   - We mentioned syndromes associated with abnormal levels of cortisol in the first lecture, and we said that abnormally high levels of cortisol cause Cushing syndrome and abnormally low levels of cortisol cause Nelson syndrome
   - Causes:
     A. Exogenous: (iatrogenic) (patient takes cortisol)
     B. Endogenous: (less common)
        - ACTH-dependent:
          - ✓ ACTH-secreting PA (pituitary adenoma)
          - ✓ Ectopic ACTH production
        - ACTH-independent:
          - ✓ Primary adrenal adenoma
          - ✓ Adrenal carcinoma
          - ✓ Primary adrenal hyperplasia
          - ✓ Micronodular bilateral adrenal hyperplasia
   - Clinical symptoms of Cushing disease:
     A. Hypertension (Blood pressure)
     B. Fat distribution: central obesity (abdomen + back), moon face (face), buffalo hump (back + neck) (buffalo hump is a term that refers to a collection of excess fat behind the neck that causes the shoulders to develop a hump-like shape)
     C. Hyperglycemia: high blood sugar, affects people with diabetes (natural antagonist to insulin)
     D. Glucoseurea: excretion of glucose into the urine
     E. Polyuria: excessive urination
     F. Polydipsia: excessive thirst or excess drinking
     G. Prximal muscle weakness (atrophy)
     H. Bone resorption (osteoclast activation) (osteoporosis) (Osteoporosis is a systemic skeletal disorder characterized by low bone mass)
     I. Collagen degradation, which causes:
        - Thin skin
        - Easy bruise
        - Poor wound healing
        - Striation
     J. Hisrutism (Hirsutism is excessive body hair on parts of the body where hair is normally absent or minimal) (increased level of cortisol -> increased level of androgen -> increased hair growth)
     K. Menstrual abnormalities
     L. Immune suppression (depleted level of T cells)
     M. Mental and psychotic disturbances

❖ ACTH-secreting PA:

- most common cause of endogenous hypercortisolism = Cushing syndrome (60%)
- more common in women and young adults
- functional (hormone-secreting) microadenoma (≤1cm)
- Adrenal glands show bilateral nodular hyperplasia (multiple lumps in the adrenal glands, on both sides, cause adrenal gland enlargement (hyperplasia) and result in the production of higher-than-normal levels of cortisol)

❖ Ectopic ACTH production:

- Ectopic ACTH syndrome is when a tumor in our body makes ACTH but not in the part of body where its supposed to be. Normally ACTH is made in the pituitary gland, but in this case, the tumor is somewhere else in the body.
- 5-10% of endogenous Cushing syndrome cases
- More common in men, middle age
- Causes for ectopic ACTH production / tumors which produce ACTH:
  A. Small cell carcinoma of lung
  B. carcinoid tumor (A carcinoid is a slow-growing type of neuroendocrine tumor originating in the cells of the neuroendocrine system) (Neuroendocrine cells have traits similar to nerve cells and to hormone-producing cells)
  C. medullary carcinoma of thyroid (rare cancer that originates from the parafollicular cells or C cells of the thyroid gland)
  D. pancreatic neuroendocrine tumors
- In some cases, ectopic production of CRH (Corticotropin-releasing hormone secreted by the paraventricular nucleus of the hypothalamus in response to stress)
- bilateral adrenal nodular hyperplasia (multiple lumps in the adrenal glands, on both sides, cause adrenal gland enlargement (hyperplasia) and result in the production of higher-than-normal levels of cortisol)
- Pathologic changes is less prominent than pituitary cause, secondary to poor prognosis of accompanied cancer

❖ Primary adrenal adenoma:

- 10-20% of ACTH-independent cases
- More common in women
- Low ACTH level (negative feedback on pituitary) (negative feedback limits pituitary secretion of hormones including ACTH)
- PRKAR1A genetic mutation (The PRKAR1A gene provides instructions for making a subunit of the enzyme protein kinase A, which promotes cell growth and division (proliferation))
- The other adrenal gland is atrophic (Atrophy is the partial or complete wasting away of a part of the body) (one has adenoma and the other is atrophic)
- Adrenal gland is <30 g (normally their combined weight in an adult human ranges from 7 to 10 grams)
- Non-functional (non-hormone producing) adrenal adenoma is more common

❖ Adrenal carcinoma:

- 5-7% of ACTH-independent cases
- Very large size of adrenal glands

- The adrenal gland is >200 g (huge)
- The other adrenal gland is atrophic (one has carcinoma and the other is atrophic)
- Produces very high level of cortisol
- Genetic mutations in:
  A. activation of beta-catenin (CTNNB1) (involved in regulation and coordination of cell–cell adhesion and gene transcription)
  B. inactivation of TP53 (tumor suppressor gene), MEN1 (tumor suppressor associated with multiple endocrine neoplasia type 1) and PRKAR1A (The PRKAR1A gene provides instructions for making a subunit of the enzyme protein kinase A, which promotes cell growth and division (proliferation))

❖ Primary adrenal hyperplasia:
- Independent of ACTH
- Rare
- Shows bilateral adrenal cortical hyperplasia (multiple lumps in the adrenal glands, on both sides, cause adrenal gland enlargement (hyperplasia) and result in the production of higher-than-normal levels of cortisol)
- nodules are larger than 1 cm (macronodular)
- types:
  A. Familial disease: : inherited mutation in the tumor suppressor gene: armadillo repeat containing 5 (ARMC5)
  B. Sporadic disease:
     ✓ 50% show ARNC5 mutation (plays an important role in adrenal tumorigenesis)
     ✓ ectopic production of G-protein coupled hormone receptors (similar action of ACTH)
  C. Syndromic disease = McCune Albright syndrome:
     ✓ a complex genetic disorder affecting the bone, skin and endocrine systems = multisystemic disease
     ✓ arises from germline activating mutation in GNAS (GNAS stands for Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide) (the gene's main product is the heterotrimeric G-protein alpha subunit Gs-α)
     ✓ leads to excessive production of cAMP (G protein-coupled-receptor signaling pathway leads to production of cAMP)

❖ Micronodular bilateral adrenal hyperplasia:
- ACTH-independent
- Small nodules (<1 cm) (small balls appearance)
- Two variants:
  A. primary pigmented nodular adrenocortical disease
  B. Carney complex (multisystemic disease of endocrine and non-endocrine neoplasms)
- Both variants harbor mutation in cAMP-dependent protein kinase (PRKAR1A gene)-> producing excessive cAMP

2. PRIMARY HYPERALDOSTERONISM:

- is due to a problem of the adrenal glands themselves, which causes them to release too much aldosterone.
- Chronic excessive production of aldosterone
- Patients develop:
  A. Hypertension
  B. Hypokalemia (low level of potassium in the blood serum)
  C. suppression of renin-angiotensin system (Renin-angiotensin system is a hormone system that regulates blood pressure and fluid balance) (low level of renin)
  D. decreased renin activity (renin plays the main role in the body's parameter of blood pressure, thirst, and urine output)
- Primary hyperaldosteronism is caused by one of three diseases:
  A. Bilateral idiopathic hyperaldosteronism (60%)
  B. Adrenocortical neoplasm (35%)
  C. Familial hyperaldosteronism (5%)

❖ Bilateral idiopathic hyperaldosteronism:
- Bilateral nodular hyperplasia of zona glomerulosa cells (The zona glomerulosa is located just beneath the capsule of the adrenal gland and contains cells which produce aldosterone that is important for sodium and water reabsorption) (hyperplasia of zona glomerulosa cells will lead to excessive production of aldosterone)
- Most commonly sporadic
- Target: old patients
- Causes: mild hypertension
- Germline mutation in KCNJ5 (potassium channel gene)
- Morphology: diffuse enlargement of the adrenal gland, sometime subtle and not obvious

❖ Adrenocortical neoplasm:
- Functional (hormone-producing) adenoma or carcinoma
- Conn syndrome: adrenal adenoma that secretes aldosterone only, more common in middle-age women
- 50% harbor KCNJ5 mutation, which encodes potassium channel on zona granulosa cells (called GIRK4 protein), mutant protein allows influx of sodium and activation of aldosterone synthase enzyme, a protein expressed only in the zona glomerulosa of the adrenal cortex and helps produce the hormone aldosterone
- Morphology:
  - ✓ adenoma is small
  - ✓ more common on left adrenal
  - ✓ buried within the gland (difficult to be seen in radiology)
  - ✓ yellow in color and resemble fasciculata cells (zona fasciculata: a zone in the adrenal cortex which contains cells that produces glucocorticoids, which regulate the metabolism of glucose)
  - ✓ Spironolactone bodies: intracellular eosinophilic material following treatment with antihypertensive (to treat hypertension) drugs
- The other adrenal gland is NOT atrophic (unlike with Cushing syndrome (the other gland IS atrophic))

❖ Familial hyperaldosteronism:
- Four subtypes
- FH-1 (familial hyperaldosteronism – type 1) = glucocorticoid-remediable aldosteronism:
  - ✓ mutation in CYP11B2 (encoding aldosterone synthase)
  - ✓ becomes sensitive to ACTH (ACTH can induce aldosterone production)
- The other four subtypes are rare

3. SECONDARY HYPERALDOSTERONISM:
- is caused by something outside the adrenal glands.
- Activation of renin-angiotensin system
- Increased level of plasma renin, occurs in:

A. Decreased renal perfusion (reduced blood flow to kidney), due to :
- (renal artery stenosis (narrowing of one or both of the renal arteries)
- arteriolar nephrosclerosis (progressive impairment of the kidneys due to poorly controlled blood pressure)

B. Arterial hypovolemia (low blood volume) and edema, due to:
- congestive heart failure (long-term condition in which your heart can't pump blood well enough to meet your body's needs)
- cirrhosis (severe scarring of the liver)
- nephrotic syndrome (is a collection of symptoms due to kidney damage)

C. Pregnancy (estrogen-induced) (Estrogen stimulates the renin-angiotensin system by increasing levels of angiotensinogen and renin in peripheral tissues and blood circulation)

4. ADRENOGENITAL SYNDROMES:
- Related to sex hormones
- Normally, the adrenal glands secrete dehydroepiandrosterone and androstenedione which converts to testosterone (male sex hormone)
- Secretion is ACTH-dependent
- Adrenocortical neoplasm associated with virilization (the development of male physical characteristics):
  - carcinoma is more common than adenoma
  - can be pure or mixed with hypercortisolism

5. CONGENITAL ADRENAL HYPERPLASIA:
- Excessive production of sex hormones
- Group of autosomal recessive disorders (autosomal: inheritance of a gene located on a non-sex chromosome) (recessive: two copies of the mutated gene are needed to cause the disorder)
- Deficiency in enzymes responsible for synthesizing cortisol
- Steroid precursors accumulate and shifts to synthesis of androgens resulting in virilization (the development of male physical characteristics) (there is a deficiency in the enzymes which synthesize cortisol, which is a steroid hormone (glucocorticoid), so the steroid

precursors (material used to synthesize cortisol) will accumulate, and the body's response to that is to synthesize androgens, which will result in increasing it level, leading to increased appearance of male characteristics such as deep voice, body hair, etc)

- Maybe associated with deficiency in aldosterone synthesis, too
- 21-hydroxylase deficiency:
    - The most common deficiency (90%)
    - mutation in CYP21A1 gene (encodes a protein for metabolizing xenobiotic and some drugs)
    - variable degree of deficiency
    - Morphology:
        - ✓ bilateral nodular hyperplasia of adrenals
        - ✓ brown
        - ✓ hyperplasia of pituitary corticotroph cells (cells in the anterior pituitary which produce POMC - pro-opiomelanocortin)
    - results in either:
        A. Salt wasting syndrome:
            - ✓ different conditions that affect the body's ability to absorb and reabsorb sodium, leading to low sodium levels in the blood (hyponatremia) and low fluid volume
            - ✓ associated with deficiency in:
                - ➢ aldosterone
                - ➢ cortisol
                - ➢ catecholeamine synthesis (monoamine neurotransmitters)
            - ✓ appears in utero or shortly after birth
            - ✓ patient suffers from:
                - ➢ hyponatremia: low level of sodium in the blood serum
                - ➢ Hypokalemia: low level of potassium in the blood serum
                - ➢ Hypotension: low blood pressure
                - ➢ cardiovascular collapse: loss of sufficient cerebral blood flow to maintain consciousness
                - ➢ virilization in females: development of male physical characteristics

        B. Simple virilization:
            - ✓ no salt wasting (normal sodium levels in blood, normal fluid volume)
            - ✓ genital ambiguity: external genitals don't appear to be clearly either male or female

        C. Late-onset adrenal virilism:
            - ✓ Common
            - ✓ partial enzyme deficiency, leads to:
                - ➢ hirsutism: excessive growth of dark hair in a male-like pattern
                - ➢ acne
                - ➢ irregular menses (abnormal menstruation = irregular periods)

6. ADRENOCORTICAL INSUFFICIENCY:

- A condition in which the adrenal glands do not produce enough amounts of steroid hormones
- Could be:
  A. Primary, due to: adrenal failure (acute or chronic)
  B. Secondary, due to: ACTH deficiency (hypopituitarism)
- Primary acute adrenocortical insufficiency, Caused by:
  - sudden withdrawal of exogenous steroids
  - massive adrenal hemorrhage (newborns, difficult delivery and hypoxia (low level of oxygen))
  - Coagulopathy: a condition in which the blood's ability to coagulate (form clots) is impaired, which leads to prolonged or excessive bleeding.
- Waterhouse-Friderichsen syndrome: overwhelming bacterial infection (classically occurs in Neisseria meningitidis), leads to direct injury to adrenal vessels resulting in hemorrhage and damage to adrenals.

7. PRIMARY CHRONIC ADRENOCORTICAL INSUFFICIENCY (Addison disease):
   - Progressive destruction of adrenal cortex
   - Uncommon
   - Symptoms appear after 90% damage to adrenocortical tissue
   - Causes:
     A. autoimmune inflammation
     B. Infections (HIV, TB)

8. PHEOCHROMOCYTOMA:
   - Tumor of adrenal medulla (chromaffin cells: neuroendocrine ceels, they are the body's main source of circulating catecholamines)
   - Secretes catecholamines
   - results in hypertension
   - variants:
     A. 10% bilateral
     B. 10% biologically malignant
     C. 10% not associated with hypertension
     D. 10% arises in extra-adrenal sites (not in the adrenal gland), such as: (carotid body, called paraganglioma: neuroendocrine neoplasm that may develop at various body sites)
     E. 10% familial (early-life onset)
   - Caused by: Genetic mutations in:
     A. growth-factor receptor pathway genes (RET, NF1)
     B. increased activity of hypoxia-induced transcription factors (HIF-1α , HIF-2α)
   - Morphology:
     - variable size
     - may show necrosis
     - bleeding

    - incubation with potassium dichromate produces dark brown color (chromaffin)
- Histology: (zellballen pattern): small nests of cells separated by supporting sustentacular cells (a type of cell primarily associated with structural support, they can be found in various tissues)
- Malignancy is determined by the presence of metastasis, not histology

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